REMARKS

In the previous Action of the parent application, all of the Claims were rejected under 35 U.S.C. §103(a) as being unpatentable over Singer et al. in view of Rork et al. and Kim. Applicants respectfully traverse.

In that Action, the Office admitted that

> . . . Singer et al. does not expressly teach the dosage unit is formulated as a once-a-day dosage unit. Singer et al. does not expressly teach to incorporate the β-blockers and statin cholesterol reducing agents herein into a single dosage unit consisting essentially of the same.

In fact, the Office specifically admits that none of the references teach combining the multiple medications into a single dosage unit. The Office, on the other hand, relies on its rejection by stating that one of ordinary skill in the art would have been motivated to incorporate any of the medications into a single medicament dosage unit because combining two agents which are known to be useful to reduce the risk of developing cardiovascular disease individually into a single composition useful for the very same purpose is prima facie obvious. At least additive therapeutic effects would be reasonably expected.

The Office misunderstands the teaching of Applicants' disclosure and the problems that Applicants' invention is attempting to solve. This is clear from the Office's statement that "it is applicant's burden to demonstrate unexpected results over the prior art." This would be true if Applicants' invention was attempting to show or teach "additive therapeutic effects." However, this is not the purpose of Applicants' invention.

Applicants respectfully direct the Office's attention to Applicants' disclosure.

Applicants disclose that beta-blockers and cholesterol-lowering medications exist in the prior art. All of the prior art cited by the Office reinforces the idea that these medications exist in the prior art. Applicants do not presume to claim that these medications are new. Nor do Applicants presume or teach in their disclosure that combining these medications provides an additive therapeutic effect. Applicants' invention contemplates an interventional measure that is neither within the scope of lay individuals nor presently available to lay individuals. As discussed in Applicants' disclosure as well as the various publications referenced in previous office actions, there is a need for cardiovascular preventive treatment and a need to overcome a failure of patients to avail themselves of such treatment. This underscores the need for the formulations of the present invention. Combining these agents to provide a single dosage unit for a user would simplify treatment, increase convenience, reduce cost, and enhance compliance with the use of medications that require long-term use.

The Office admits that none of the prior art cited by the Office expressly teaches the combination of medications in a single dosage unit to enhance compliance, simplify treatment, increase convenience, and reduce cost. The Office presumes that "one of ordinary skill in the art would have been motivated to incorporate all agents herein together in a single dosage unit because they are known to be useful for the same purpose, i.e. for treatment of hypertensive patients and reduction of the risk of cardiovascular events. The Office's conclusion is wrong. It is wrong because the Office's premises are faulty and it is wrong because it is contrary to the requirements of law.

Faulty Premis

Applicants' invention is not designed to claim a combination that provides an additive therapeutic effect, which may require the showing of unexpected results. Applicants' invention was conceived to provide the claimed cardiovascular medicaments in a single dosage unit for a user to help alleviate existing and on going, long-term problems. Specifically, Applicants' invention is an attempt to simplify treatment, increase convenience, reduce cost, and enhance patient compliance, particularly in older patients where cardiovascular treatment regimens require taking multiple medications over long-term treatment periods.

Not only does Applicants' invention represent an attempt to provide a prophylactic therapy in a single dosage unit to address the above-mentioned problems, but Applicants' invention also attempts to improve upon the under-utilization of these specific medications, namely beta-blockers and cholesterol-lowering agents. Under-utilization is clearly a concern of the medical profession. Particularly, health plan organizations are continually looking for effective ways to improve health outcomes and lower costs.

Dr. Herbert M. Dean's declaration is submitted herewith in support of the above conclusions. Dr. Dean has extensive experience in the healthcare industry including experience as President of a major health plan, Fallon Community Health Plan. Dr. Dean is well aware of the problems that exist in healthcare, particularly with the under-utilization of cardiovascular medications. To support Dr. Dean's declaration, Dr. Dean

provides exhibits relating to this under-utilization problem. One exhibit is a study/investigation by McCormick et al. entitled "Use of aspirin, beta-blockers and lipid lowering medications before recurrent acute myocardial infarction: Missed opportunities for prevention?", Arch Intern Med, Vol 15, March 22, 1999, pages 561-567. This study addresses the concern that beta-blockers and lipid lowering medications are under utilized. A second exhibit is a report from Hedis 2000, a publication that reports upon the quality of health care in the United States. It states that only 10% of MCOs (managed care organizations) had an acceptable rate of beta-blocker treatment after a heart attack. The report concluded that if the remaining organizations that were studied performed similarly, more than 2000 cardiac deaths and tens of millions of dollars would be reduced annually. Dr. Dean's declaration reinforces the fact that these problems have existed for some time and continue to exist. Further, the solutions to problems with compliance and under-utilization of helpful medications for cardiovascular treatments are elusive, and have troubled the healthcare industry for a long time. The industry continues to struggle to find answers to these perplexing questions. The healthcare industry's focus is now and has always been to educate physicians and patients, not to providing novel means for achieving better patient compliance and utilization results.

The present application specifically addresses the failure of patients to receive these treatments and seeks to improve it, as stated on Page 5, lines 21-24 of Applicants' disclosure:

> The clear need for cardiovascular preventive treatment and the failure of patients to avail themselves of such treatment underscores the present

need for the formulations of this invention.

Nowhere in any of the cited prior art is it suggested to combine these multiple medicaments into a single dosage unit to simplify treatment, increase convenience, reduce cost and enhance patient compliance. The Office admits that none of the prior art provides the motivation to combine beta-blockers and cholesterol-lowering agents into a single dosage unit.

Applicants further submit that the cited references merely recite cardiovascular medications and contain no teaching or suggestion relating to the failure of patients to receive particular treatments. The references cited neither acknowledge this problem nor contain any suggestion for improving upon it. The haphazard combining of medications, even those known to have cardiovascular usage, would not improve upon this problem.

The Office notes that one of ordinary skill in the art would have been motivated to incorporate beta-adrenergic blockers and cholesterol lowering agents, expecting at least additive therapeutic effects. This particular statement makes clear that even the Office has overlooked the rationale for the present invention, namely to improve upon the failure of patients to receive particular treatments (not trying to achieve additive effects). Similarly, this problem has been overlooked by the pharmaceutical industry despite considerable motivation, i.e. increased sales, to increase usage of medication.

Applicants submit that without some teaching or suggestion in the prior art that addresses solutions to the problem of the failure of patients to receive specific cardiovascular treatments, the present invention would be obvious only in hindsight.

Requirem nts of Law

It is clear from Applicants' disclosure that Applicants' invention is a combination of old elements. In determining obviousness, "the inquiry is not whether each element existed in the prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed." Hartness International, Inc. v. Simplimatic Engineering Co., 819 F.2d 1100, 2 USPQ2d 1826 (Fed. Cir. 1987). If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit one to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.' In re Rouffet, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). When the patented invention is made by combining known components to achieve the new system, the prior art must provide a suggestion or motivation to make such a combination. Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068 (Fed. Cir. 1994). It is insufficient that the prior art shows similar components, unless it also contains some teaching, suggestion, or incentive for arriving at the claimed structure. Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931 (Fed. Cir. 1990). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention. Smiths Industries Medical Systems, Inc. v.

Vital Signs, Inc., 50 USPQ2d 1641, *superseded on rehearing*, 183 F.3d 1347, 51 USPQ2d 1415 (Fed. Cir. 1999).

It is clear that when Applicants' invention is viewed as a whole the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications into a single dosage unit. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. In fact, the Office admits that the prior art does not provide this teaching, suggestion or motivation. The Office states that one of ordinary skill in the art would have been motivated to combine the medications into a single dosage unit because they are known to be useful for the same purpose. The Office relies on its conclusion based on In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

The Office's reliance is misplaced and Kerkhoven is inapposite. Kerkhoven is a process claim case and cites to In re Crockett, 279 F.2d 274 (CCPA 1960), which contains the reference that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful **for the same purpose**, in order to form a third composition which is to be used for the **very same purpose**. The ruling is based on the use of two compositions, each of which promotes the formation of a nodular structure in cast iron. The ruling in Kerkhoven is inappropriate in the present application because the two compositions of the present application are not used for the **v ry sam purpose**. The purpose of beta-blockers is to block nerve impulses to

special sites (beta receptors) and to reduce the rate of heartbeats and the force of heart contractions. The purpose of cholesterol-lowering agents is to reduce or prevent the deposit of arterial plaque along the walls of the arteries by suppressing total cholesterol in the blood. In other words, beta-blockers cannot be used for reducing total blood cholesterol. Where the purpose of beta-blockers and cholesterol-lowering agents are **not the same**, Kerkhoven is inapposite.

In accordance with the more recent rulings of the Federal Circuit, the Office must point to some teaching, suggestion or incentive in the cited prior art for arriving at the claimed structure. The Office has failed to do this. In fact, the Office admits that the prior art does not teach the use of beta-blockers and cholesterol-lowering agents in a single dosage unit.

In light of the above arguments, Applicants respectfully submit that Claims 1-16 of the present application contain patentable subject matter. Allowance of Claims 1-16 is therefore respectfully requested.

The Office is invited to telephone the undersigned if such communication would facilitate advancement of the present application and place it in condition for allowance.

Respectfully submitted,

Dated: 5/21/02

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on:

May 21, 2002

Robert R Deleault

Robert R Deleault

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Claim 11 has been amended as follows:

11. (Amended) A self-treatment method [of treating cardiovascular disease with] for reducing the risk of coronary heart disease using the dosage unit of Claim 1, said method comprising:

providing to a patient having said cardiovascular disease said single formulation medicament dosage unit; and

self-administering said single dosage unit.

Use of Aspirin, β-Blockers, and Lipid-Lowering Medications Before Recurrent Acute Myocardial Infarction

Missed Opportunities for Prevention?

Danny McCormick, MD, MPH; Jerry H. Gurwitz, MD; Darleen Lessard, MS; Jorge Yarzebski, MD, MPH; Joel M. Gore, MD; Robert J. Goldberg, PhD

Background: For patients who have had a previous myocardial infarction (MI), the use of aspirin, β-blockers, and lipid-lowering agents reduces the risk of recurrent MI and death.

Objective: To examine trends in and determinants of receipt of these 3 medications before hospitalization for recurrent acute MI (AMI).

Methods: The study population consisted of 1710 patients with a previous history of MI hospitalized with a validated recurrent AMI in all hospitals in Worcester, Mass, during 1986, 1988, 1990, 1991, 1993, and 1995. Logistic regression analyses were used to assess the effect of demographic, clinical, and temporal factors on the receipt of aspirin, β-blockers, and lipid-lowering medications before hospital admission for recurrent AMI.

Results: More than 47% of patients in each study year were not receiving each medication before admission, although significant increases in use were noted over time for aspirin (from 13.5% to 52.6%), β-blockers (from 33.2% to 44.4%), and lipid-lowering medications (from 0.8% to 11.7%). In multivariate analyses, advancing age was associated with not receiving aspirin (odds ratio [OR], 0.67; 95% confidence interval [CI], 0.51-0.89), lipid-lowering medications (OR, 0.14; 95% CI, 0.08-0.25), and β-blockers (OR, 0.75; 95% CI, 0.57-1.00), although this effect was of borderline significance for β-blockers. Being a woman was associated with not receiving aspirin (OR, 0.78; 95% CI, 0.62-0.98) but was positively associated with receiving lipid-lowering medications (OR, 1.59; 95% CI, 1.04-2.43). Coexisting medical conditions and concurrent use of other cardiovascular medications were also associated with receipt of each medication.

Conclusion: Despite encouraging increases over time, the low absolute levels of receipt of medications shown to be efficacious in the long-term treatment of patients after an MI, and their variation by age and sex, suggest that substantial opportunities may exist to prevent recurrent AMIs through the increased use of aspirin, β-blockers, and lipid-lowering medications.

Arch Intern Med. 1999;159:561-567

From the Section for Health Services Research, Divisions of General Medicine/Primary Care/Geriatrics (Drs McCormick, Gurwitz, Yarzebski, and Goldberg) and Cardiovascular Medicine (Ms Lessard and Drs Yarzebski, Gore, and Goldberg), and the Meyers Primary Care Institute (Drs McCormick, Gurwitz, and Goldberg), University of Massachusetts Medical Center and the Fallon Healthcare System, Worcester.

MORTALITY associated with a recurrent acute myocardial infarction (AMI) is appreciably higher than that associated with a first AMI. Several medications exist, however, that have been shown to reduce the likelihood of recurrent AMI and death in patients who have established coronary artery disease, including patients who have had an initial AMI. The effectiveness of therapy with aspirin,[1-3] β-blockers,[3-9] and lipid-lowering medications[10-12] in the secondary prevention of AMI has been well established in large, randomized clinical trials and/or meta-analyses of the published literature. It has been estimated that use of these medications can reduce the risk of cardiovascular death and nonfatal reinfarction, respectively, by 22% and 27% for β-blockers,[3,8] 13% and 31% for aspirin,[2] and 14% and 25% for all lipid-lowering medications combined.[13] Based on this evidence, widely publicized guidelines strongly recommend the routine long-term use of aspirin and β-blockers[14,15] in patients who recently had an AMI and lipid-lowering medications in patients with elevated cholesterol levels following hospital discharge after AMI.[13,16]

Despite the positive findings of studies examining the effectiveness of these therapies and the widespread dissemination of these practice guidelines, findings of several previous studies[17-23] suggest that these medications are underprescribed to patients at hospital discharge after an AMI. Results of previous studies also suggest that nonclinical factors such as age,[17,21] sex,[20] and type of medical insurance[20] may affect the likelihood of receiving these medications at hospital discharge after an AMI.

PATIENTS AND METHODS

This investigation was conducted as part of the Worcester Heart Attack Study, a multihospital, population-based investigation of time trends in the attack and survival rates associated with AMI.[24-28]

STUDY POPULATION

The population studied consisted of patients hospitalized with a primary or secondary diagnosis of AMI (*International Classification of Diseases*, Ninth Revision, code 410)[29] in all acute care general hospitals in the Worcester (Mass) Standard Metropolitan Statistical Area (1990 census estimate = 437 000) during 1986, 1988, 1990, 1991, 1993, and 1995, who had a history of myocardial infarction (MI). Sixteen university-affiliated and community hospitals were originally included in this study, with fewer hospitals included in recent study years because of hospital closures or conversions to long-term care facilities. The medical records of greater Worcester residents with a discharge diagnosis of AMI from these hospitals were individually reviewed and validated according to pre-established diagnostic criteria that have been described previously.[30-32] In brief, these criteria included a clinical history of prolonged chest pain not relieved by nitrate therapy or rest; increased total and isoenzyme subfractions of creatine kinase or lactate dehydrogenase; and serial electrocardiographic findings of ST segment changes or Q waves typical of AMI. At least 2 of these 3 criteria needed to be satisfied for study inclusion. Presence of a previous history of MI was assessed through information provided by the patient that was documented in the medical record at hospital admission and confirmed through review of the medical record of previous hospitalization for AMI at areawide hospitals.

DATA COLLECTION

The hospital records of patients with validated AMI were abstracted for demographic (age, sex, and race) and clinical data (medical history of previous MI, angina, hypertension, diabetes, congestive heart failure, or stroke), type of medical insurance, total serum cholesterol level observed during hospitalization, and preadmission medication use (aspirin, β-blockers, lipid-lowering medications, calcium channel blockers, diuretics, warfarin sodium, antiarrhythmic medications, and digoxin). Patients were considered to be taking a medication before admission if it was listed as a current outpatient medication in the medical record on the day of hospital admission for recurrent AMI. This information was provided by patients themselves, their usual outpatient physicians, or other referring institutions, such as long-term care facilities. Outpatient medical records were not used for verification of medical regimens.

STATISTICAL ANALYSIS

Time trends in the use of aspirin, β-blockers, and lipid-lowering medications before hospitalization for recurrent AMI were analyzed by determining the percentages of patients who received each of these medications by study year. A 2-sided Cochran-Armatage test for trend was used to determine statistical significance.

Demographic and clinical correlates of receiving each medication were evaluated for the study sample (all study years combined), and relative risks and 95% confidence intervals (CIs) were calculated for each variable. These variables were used to develop separate stepwise multivariate logistic regression models with use of aspirin, β-blockers, and lipid-lowering medication as the outcome variables. Candidate variables in these analyses included race (white vs all other races), medical history (angina, hypertension, diabetes, congestive heart failure, and stroke), concurrent (preadmission) use of other medications (aspirin, β-blockers, lipid-lowering medications, calcium channel blockers, diuretics, warfarin, antiarrhythmic medications, and digoxin), medical insurance (private vs Medicare, Medicaid, and uninsured), and total serum cholesterol level observed in the hospital (≥5.17 vs <5.17 mmol/L [≥200 vs <200 mg/dL]). Complete lipid profile laboratory data were not available for study participants. Our definition of a high serum cholesterol level (total cholesterol level ≥5.17 mmol/L [≥200 mg/dL]) was used to serve as a proxy for a low-density lipoprotein cholesterol level of approximately 3.36 mmol/L or greater (≥130 mg/dL),[16] the level at which medical treatment of hypercholesterolemia in patients with established coronary heart disease is recommended by the National Cholesterol Education Project guidelines, published in 1994.[13] Variables were dropped from each model at a significance level of $P<.05$. Because of a priori importance, age (<65, 65-74, and ≥75 years), sex, and study year (with 1995 as the referent category) were forced into all models. For each model, we reported adjusted odds ratios (ORs) and 95% CIs for all variables.

However, among patients experiencing recurrent AMI, little is currently known about the use of these medications before the event. Patients who have had a previous AMI are at particularly high risk for recurrent AMI and death; patients who have recurrent AMI and are not using these medications may thus represent missed opportunities for prevention. Understanding the factors associated with receipt of these medications for patients with recurrent AMI may help to overcome obstacles to optimizing their use.

The objectives of this observational, community-wide study were (1) to examine trends over time in the percentages of patients receiving aspirin, β-blockers, and lipid-lowering medications at hospital admission for recurrent AMI and (2) to identify factors that are associated with the receipt of these agents in patients with previous AMI.

RESULTS

PATIENT CHARACTERISTICS

The total study population comprised 1710 patients, most of whom were older than 65 years, male, and white, with no private medical insurance (**Table 1**). Coexisting medical conditions were common: 43.0% had angina, 58.1% had hypertension, 34.3% had diabetes, 31.2% had a history of congestive heart failure, and 36.2% had a total cho-

Table 1. Bivariate Analysis of the Association of Various Characteristics With the Receipt of β-Blockers, Aspirin, and Lipid-Lowering Medications Before Hospital Admission for Recurrent Myocardial Infarction: Worcester Heart Attack Study, 1986-1995

Characteristics	Patients, No. (%)	Risk Ratio (95% Confidence Interval)* For Receiving Aspirin	For Receiving β-Blockers	For Receiving Lipid-Lowering Medications
Demographics				
Age, y				
<65	475 (27.8)	(Referent)	(Referent)	(Referent)
65-74	476 (27.8)	0.93 (0.79-1.08)	0.97 (0.83-1.13)	0.71 (0.49-1.03)
≥75	759 (44.4)	0.81 (0.70-0.94)	0.81 (0.70-0.94)	0.23 (0.14-0.38)
Women	685 (40.0)	0.86 (0.76-0.98)	0.96 (0.85-1.09)	0.93 (0.65-1.31)
White	1593 (93.2)	1.09 (0.84-1.41)	0.76 (0.63-0.93)	1.43 (0.64-3.18)
Private insurance	552 (32.3)	1.02 (0.89-1.16)	1.02 (0.89-1.16)	1.67 (1.18-2.35)
Medical history				
Angina	735 (43.0)	1.24 (1.10-1.40)	1.41 (1.25-1.60)	1.11 (0.79-1.56)
Hypertension	993 (58.1)	1.12 (0.99-1.27)	1.56 (1.36-1.78)	1.17 (0.82-1.66)
Diabetes	586 (34.3)	1.11 (0.98-1.26)	1.10 (0.97-1.25)	1.03 (0.72-1.47)
Congestive heart failure	534 (31.2)	0.97 (0.85-1.11)	0.80 (0.70-0.93)	0.77 (0.53-1.14)
Stroke	219 (12.8)	1.23 (1.04-1.45)	1.03 (0.86-1.24)	0.95 (0.56-1.59)
Cholesterol level, mmol/L (mg/dL)				
<5.17 (<200)	1091 (63.8)	(Referent)	(Referent)	(Referent)
5.17-6.18 (200-239)	313 (18.3)	1.10 (0.94-1.29)	1.07 (0.91-1.26)	1.54 (1.02-2.32)
≥6.21 (≥240)	306 (17.9)	0.98 (0.83-1.16)	1.12 (0.95-1.31)	1.31 (0.84-2.04)
Medication use on admission				
Aspirin	635 (37.1)	...	1.64 (1.46-1.86)	3.79 (2.62-5.48)
β-Blockers	637 (37.3)	1.65 (1.46-1.86)	...	2.02 (1.43-2.83)
Lipid-lowering medications	123 (7.2)	1.99 (1.74-2.29)	1.52 (1.27-1.81)	...
Calcium channel blockers	751 (43.9)	1.21 (1.07-1.37)	1.10 (0.97-1.25)	1.34 (0.95-1.89)
Diuretics	665 (38.9)	0.88 (0.77-1.00)	0.83 (0.73-0.95)	0.85 (0.59-1.21)
Warfarin	133 (7.8)	0.84 (0.65-1.09)	1.23 (1.01-1.50)	1.28 (0.73-2.26)
Antiarrhythmic medications	166 (9.7)	1.15 (0.95-1.39)	2.01 (1.77-2.27)	1.39 (0.84-2.29)
Digoxin	435 (25.4)	1.00 (0.86-1.15)	0.72 (0.61-0.85)	0.75 (0.49-1.14)

*Ellipses indicate not applicable.

lesterol level greater than 5.17 mmol/L [>200 mg/dL]. The percentages of patients receiving aspirin, β-blockers, and lipid-lowering medications at hospital admission were 37.1%, 37.3%, and 7.2%, respectively. Concurrent use of additional cardiovascular medications varied, ranging from 43.9% of patients taking a calcium channel blocker to 7.8% of patients taking warfarin.

RECEIPT OF ASPIRIN, β-BLOCKERS, AND LIPID-LOWERING MEDICATIONS BEFORE ADMISSION FOR RECURRENT AMI

Aspirin

The percentages of patients with AMI who were receiving aspirin at hospital admission increased significantly ($P<.001$) during the 6 study years, from 13.5% in 1986 to 52.6% in 1995 (**Figure 1**). Older patients and women were significantly less likely to be receiving aspirin, whereas patients who had a history of angina or stroke or who were concurrently receiving β-blockers, lipid-lowering medications, or calcium channel blockers were more likely to be receiving aspirin (Table 1).

In the multivariate regression model, 10 demographic and clinical variables were identified as having an independent association with receiving aspirin at hospital admission (**Tabl 2**). Enrollment in earlier study years (compared with more recent study years) was associated with not receiving aspirin (OR, 0.13; 95% CI, 0.09-0.21; comparing 1986 with 1995). Advancing patient age (OR, 0.67; 95% CI, 0.51-0.89; for age >75 years compared with age <65 years) and female sex (OR, 0.78; 95% CI, 0.62-0.98) were also associated with not receiving aspirin. As in the bivariate analysis, history of angina or stroke and concurrent use of several other cardiovascular medications, including β-blockers and lipid-lowering medications, were associated with receiving aspirin.

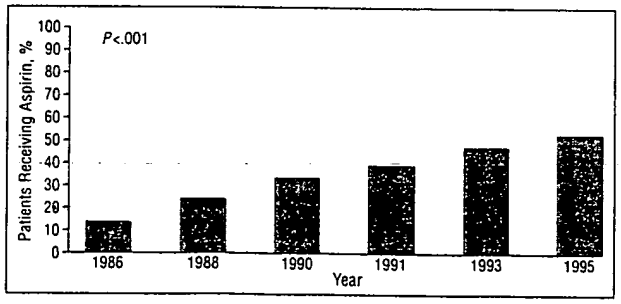

Figure 1. *Temporal trends in the receipt of aspirin before hospital admission for recurrent acute myocardial infarction: Worcester Heart Attack Study, 1986-1995.*

β-Blockers

The percentages of patients with AMI who were receiving β-blockers at hospital admission increased mod-

Table 2. Variables Predicting Receipt of Aspirin Before Admission for Recurrent Acute Myocardial Infarction: Worcester Heart Attack Study

Variable	Adjusted Odds Ratio (95% Confidence Interval)
Age, y	
<65	1.00 (Referent)
65-74	0.84 (0.64-1.11)
≥75	0.67 (0.51-0.89)
Women	0.78 (0.62-0.98)
Study year	
1995	1.00 (Referent)
1993	0.81 (0.59-1.10)
1991	0.58 (0.41-0.81)
1990	0.44 (0.31-0.63)
1988	0.29 (0.19-0.43)
1986	0.13 (0.09-0.21)
History of angina	1.30 (1.04-1.63)
History of stroke	1.41 (1.02-1.93)
Concurrent β-blocker use	2.14 (1.71-2.67)
Concurrent lipid-lowering drug use	2.61 (1.70-4.00)
Concurrent calcium channel blocker use	1.39 (1.12-1.74)
Concurrent warfarin use	0.45 (0.29-0.68)
Concurrent digoxin use	1.44 (1.12-1.87)

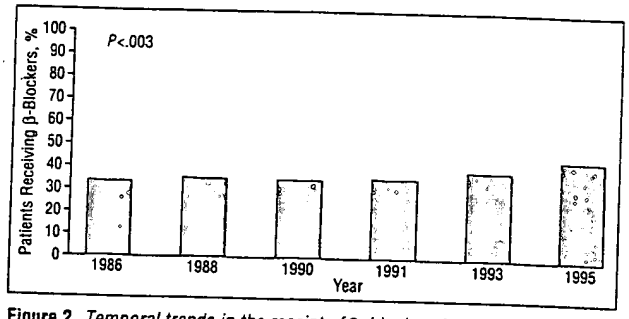

Figure 2. *Temporal trends in the receipt of β-blockers before hospital admission for recurrent acute myocardial infarction: Worcester Heart Attack Study, 1986-1995.*

estly ($P<.003$) during the 6 study years, from 33.2% in 1986 to 44.4% in 1995 (**Figure 2**). Advancing age, white race, a history of congestive heart failure, and use of diuretics or digoxin were associated with not receiving a β-blocker (Table 1). Patients with a history of angina or hypertension or who were concurrently receiving aspirin, lipid-lowering medications, warfarin, or antiarrhythmic medications were more likely to receive a β-blocker.

In the multivariate regression model, 12 demographic and clinical variables were identified as having an independent association with receiving a β-blocker (**Table 3**). Although there was a statistically significant increase in the odds of receiving a β-blocker from 1990 (OR, 0.62; 95% CI, 0.42-0.90) and 1991 (OR, 0.63; 95% CI, 0.43-0.91) to 1995, the odds of receiving this medication in earlier years (1986 or 1988) were no lower than in the most recent study year (1995). As in the bivariate analysis, advancing patient age (OR, 0.75; 95% CI, 0.57-1.00) and white race (OR, 0.53; 95% CI, 0.35-0.72) were associated with not receiving a β-blocker. History of angina or hypertension and concurrent use of other cardiovascular medications, including aspirin and lipid-lowering medications, were again positively associated with receiving a β-blocker.

Table 3. Variables Predicting Receipt of β-Blockers Before Admission for Recurrent Acute Myocardial Infarction: Worcester Heart Attack Study

Variable	Adjusted Odds Ratio (95% Confidence Interval)
Age, y	
<65	1.00 (Referent)
65-74	1.02 (0.78-1.35)
≥75	0.75 (0.57-1.00)
Women	1.05 (0.83-1.32)
White	0.53 (0.35-0.72)
Study year	
1995	1.00 (Referent)
1993	0.75 (0.54-1.05)
1991	0.63 (0.43-0.91)
1990	0.62 (0.42-0.90)
1988	0.83 (0.56-1.24)
1986	0.92 (0.63-1.36)
History of angina	1.73 (1.39-2.14)
History of hypertension	2.19 (1.75-2.76)
Total cholesterol level >5.17 mmol/L (>200 mg/dL)	1.30 (1.03-1.64)
Concurrent aspirin use	2.22 (1.76-2.78)
Concurrent warfarin use	1.72 (1.14-2.60)
Concurrent diuretic use	0.70 (0.55-0.89)
Concurrent antiarrhythmic medication use	5.25 (3.60-7.66)
Concurrent digoxin use	0.57 (0.43-0.76)

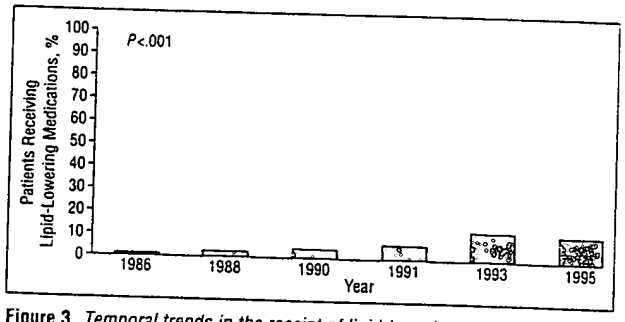

Figure 3. *Temporal trends in the receipt of lipid-lowering medications before hospital admission for recurrent acute myocardial infarction: Worcester Heart Attack Study, 1986-1995.*

Lipid-Lowering Medications

The percentages of patients with AMI who were receiving lipid-lowering medications increased significantly ($P<.001$) during the 6 study years, from 0.8% in 1986 to 11.7% in 1995 (**Figure 3**). Older patients, women, and those not covered by private medical insurance were significantly less likely to be receiving a lipid-lowering medication, whereas patients who had an elevated cholesterol level (≥5.17 mmol/L [≥200 mg/dL]) or who were concurrently receiving β-blockers or aspirin were more likely to be receiving a lipid-lowering medication (Table 1). This low level of receipt of lipid-lowering medications was despite the finding that more than 36.2% of patients had a total cholesterol level greater than 5.17 mmol/L (>200 mg/dL) (Table 1).

Table 4. Variables Predicting Receipt of Lipid-Lowering Medications Before Admission for Recurrent Acute Myocardial Infarction: Worcester Heart Attack Study

Variable	Adjusted Odds Ratio (95% Confidence Interval)
Age, y	
<65	1.00 (Referent)
65-74	0.60 (0.39-0.93)
≥75	0.14 (0.08-0.25)
Women	1.59 (1.04-2.43)
Study year	
1995	1.00 (Referent)
1993	1.11 (0.68-1.80)
1991	0.44 (0.23-0.84)
1990	0.29 (0.14-0.60)
1988	0.16 (0.06-0.44)
1986	0.07 (0.02-0.30)
Total cholesterol level >5.17 mmol/L (>200 mg/dL)	1.77 (1.16-2.69)
Concurrent aspirin use	2.85 (1.88-4.32)
Concurrent calcium channel blocker use	1.53 (1.03-2.27)

In the multivariate regression model, 6 demographic and clinical variables were identified as having an independent association with receiving a lipid-lowering medication (**Table 4**). Enrollment in earlier study years was associated with not receiving a lipid-lowering medication. Advancing patient age (OR, 0.14; 95% CI, 0.08-0.25) also remained associated with not receiving a lipid-lowering medication. An elevated serum cholesterol level and concurrent use of other cardiovascular medications were, as in the bivariate analysis, also associated with receipt of a lipid-lowering medication. In contrast to the bivariate analysis, women were significantly more likely to be receiving a lipid-lowering medication after controlling for demographic and clinical factors.

COMMENT

Evidence-based clinical guidelines strongly endorse the use of aspirin and β-blockers in nearly all patients who have experienced an MI and do not have specific contraindications[14,15] and the use of lipid-lowering medications in those with elevated serum cholesterol levels.[13,16] Studies establishing the efficacy of using these medications for secondary prevention in coronary heart disease, on which these practice guidelines are based, were published before the first year of the present investigation. Despite widespread dissemination of this information, we found that, even by 1995, more than half of all patients who were first seen with recurrent AMI were not receiving aspirin or a β-blocker and that most patients (>90%; two thirds of those with an elevated cholesterol level) were not receiving a lipid-lowering medication. Although receipt of aspirin and lipid-lowering medications increased substantially during the approximately 10-year study, only modest changes were noted for β-blocker use. In addition to comorbidities and concurrent cardiovascular medication use, receipt of these medications was significantly affected by nonclinical factors such as age and sex. These findings suggest substantial missed opportunities for the prevention of recurrent AMI with the use of these effective therapies.

Results of well-designed clinical trials have been shown to affect the prescription of cardiovascular medications by physicians.[28,33] However, results of several previous studies conducted in the 1990s found significant underuse of aspirin[17-19] and β-blockers[18,20-23] at hospital discharge after an initial AMI despite the demonstrated efficacy of these medications in published clinical trials. Undertreatment of hypercholesterolemia among patients with established coronary heart disease also has been previously described.[34] The low rates of prescribing these medications have been attributed to deficits in physician knowledge of medication effectiveness because of long delays in the dissemination of the results of clinical research to practicing clinicians.[22,34-38] For example, results of a recent study[38] show that the time lag between published meta-analyses that established the efficacy of using aspirin and β-blockers in the secondary prevention of MI and the recommended use of these medications by more than half the authors of review articles and textbook chapters on the subject was 6 and 2 years, respectively. In addition, despite the publication of evidence-based practice guidelines recommending treatment of hypercholesterolemia for patients with established coronary heart disease in 1988,[16] the use of lipid-lowering medications was not yet recommended by more than half the authors of review articles and textbook chapters on the subject 2 years later.[38] This considerable time lag between the publication of results of clinical trials and the acquisition of this knowledge by physicians may be largely responsible for the low percentages of patients receiving aspirin, β-blockers, and lipid-lowering medications that we observed and the dramatic increases in receipt of aspirin and lipid-lowering medications years after their effectiveness was first demonstrated.

We also found that, although aspirin, β-blockers, and lipid-lowering medications were received by relatively small percentages of patients after an MI, these medications were received at even lower levels by several clinically and demographically defined patient subgroups. As expected, patients with cardiovascular risk factors and comorbid conditions tended to be more likely to be receiving any one of the 3 medications of interest, and patients who were currently using any 1 of these medications were more likely to be using another of them. However, nonclinical factors such as age and sex also affected patterns of receipt of these medications. Patients who were older (≥75 years) were significantly less likely to use any of the 3 medications, a finding consistent with previous studies that show underuse of β-blockers[20-22] and aspirin[17] in elderly patients at hospital discharge after AMI. Yet, the survival benefit from β-blocker[21,39] and aspirin[1] therapy in patients with established coronary heart disease appears to be at least as great for elderly as nonelderly patients. The benefits of therapy with lipid-lowering medications in elderly patients with established coronary heart disease have not been clearly demonstrated because most large clinical trials do not include adequate numbers of elderly patients. Nonetheless, because there is no evidence that the basic pathophysiological processes underlying coronary atherogenesis

are different for elderly and nonelderly patients, National Cholesterol Education Program guidelines recommend that age alone should not be a reason to treat hypercholesterolemia less aggressively.[13]

Women in the present population-based study were significantly less likely to be receiving aspirin at the time of reinfarction, a finding consistent with that of a previous study[40] showing that aspirin is used less often for women than for men after an initial MI. As with increasing age, results of previous research do not suggest a less beneficial effect of aspirin use in women than in men with previous MI.[1] However, in our multivariate models, being a woman was associated with greater odds of receiving a lipid-lowering agent. Thus, patient sex seems to have a variable effect on the odds of receiving effective therapies at the time of recurrent AMI.

Lack of physician awareness of the results of clinical trials demonstrating the effectiveness of these medications or of practice guidelines recommending the use of these medications irrespective of age or sex may contribute to the low percentages of patients receiving these medications that we observed. It is also likely that use of these 3 medications was affected by the presence of clinical contraindications. β-blocker use is contraindicated in patients with heart block, bradycardia, congestive heart failure, reactive airways disease, diabetes mellitus, and depression, and aspirin use may be contraindicated in patients with bleeding disorders, peptic ulcer disease, thrombocytopenia, and aspirin allergy. Use of lipid-lowering medications is contraindicated in few patients. Because data were only available for a few coexisting illnesses that could constitute a contraindication to medication use, we could not assess the magnitude of the impact of clinical contraindications on the rates of use of these medications. However, of patients screened for possible inclusion in the largest β-blocker trials, the proportion who had contraindications to β-blocker use did not exceed 18%.[7,41] In a previous aspirin trial,[42] the percentage of screened patients who were excluded because of contraindications to aspirin use was less than 4%. Although it is possible that patients with recurrent AMI may have more contraindications to medication use than patients in these clinical trials, it seems unlikely that such differences could completely account for the low medication use rate that we observed.

Beyond physician prescribing practices, the patient's inability to comply with physician recommendations may contribute to lower use rates. It is possible that the cost of long-term therapy may discourage some patients from continuing to use these medications. We found that patients with private insurance were more likely to be using lipid-lowering medications, most classes of which are relatively expensive (eg, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), at the time of their recurrent MI. This relationship did not persist in the multivariate model, but it is possible that this was caused by either low statistical power because of the small number of patients using lipid-lowering medications or residual confounding by age because patients with nonprivate insurance (including Medicare) were more likely to be older. The relationship between insurance status and use of lipid-lowering medications in patients after an MI, therefore, deserves further study. For use of β-blockers and aspirin, 2 relatively inexpensive medications, we found no association with medical insurance status.

It is also likely that patients' inability to tolerate the adverse effects of these medications contributed to the low usage rates we observed. In a previous large study[41] of patients who have experienced an MI, the Beta-blocker Heart Attack Trial, withdrawal of β-blocker therapy because of adverse effects was 13% for 2 years of follow-up. In the Coronary Drug Project Research Group trial[43] of aspirin for secondary prevention, only 4.5% of patients taking aspirin were compliant with therapy less than 20% of the time during an average of 22 months of follow-up. However, results of a previous study[44] show that rates of discontinuation of lipid-lowering medication use in the primary care setting (primary and secondary prevention patients combined) were variable, depending on the particular agent prescribed, and were higher, in general, than the rates reported in clinical trials. Unfortunately, no data were collected as part of our study that would allow us to assess the impact of this problem on receipt of medications examined in this study.

Although it is likely that each factor discussed has some effect on the rate of use of these medications, physician prescribing behavior is likely to have the greatest impact. Results of previous studies on receipt of aspirin and β-blockers by patients after an MI indicate that physicians do not prescribe these medications to 15% to 25% of eligible patients at hospital discharge. Furthermore, the rapid rise in the use of aspirin and lipid-lowering medications over time in the present study more likely reflects substantial changes in physician prescribing behavior because of the acquisition of new knowledge about health benefits associated with these agents rather than dramatic changes in the prevalence of contraindications to using these medicines or changes in patients' ability to comply with recommended therapy.

Residents of the Worcester metropolitan area are similar to those of the overall United States with respect to characteristics such as age, sex, and socioeconomic status but not for race.[24,30] By including all patients hospitalized with recurrent AMI from a defined geographic area, this study minimized the likelihood of selection biases that may be present in studies of patients hospitalized in single or referral hospitals. Several limitations of this study should also be noted. First, to assess medication use just before admission, we relied on documentation of the patient's outpatient medical regimen in the medical record at hospital admission for recurrent AMI. To the extent that this information in many cases came from patient self-report, inaccuracies in patient recall could have led to some underestimates or overestimates of the rates of use of these medications.

Second, although detailed information about cardiovascular comorbidities and concurrent medication use was available for study patients, information on the complete range of additional comorbidities that could represent absolute or relative contraindications to use of the 3 medications examined was not available. In addition, information about discontinuation of medication use because of adverse effects was not known. Thus, we could not determine the "right" percentage of patients who should have been receiving each medication we examined. Third, although this study highlights the small percentages of patients receiving these medications in ac-

tual practice, we were not able to assess the reasons underlying these patterns of care. Future studies will need to address the relative impact of physicians' failure to prescribe these medications and patients' inability or choice not to comply with recommended therapies.

In summary, this study documents the extent of underuse of aspirin, β-blockers, and lipid-lowering medications by patients with a previous history of MI who later experience a recurrent AMI and identifies clinical and nonclinical factors associated with this underuse. Although the rates of use of the cardiovascular medications we studied may be higher for patients after an MI who did not have a recurrent event (to the extent that these medications are effective), our findings confirm that there remain substantial missed opportunities to treat patients after an MI with medications that are shown to reduce the risk of recurrent MI and cardiovascular death. Given the high prevalence of MI, concerted efforts should be undertaken to facilitate more rapid transmission of the results of clinical trials of cardiovascular medications to practicing physicians and to reduce substantial variation in treatment practices that seems to be related to patient age and sex.

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